Paper No. 65

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte IRVING BOIME, MARTIN M. MATZUK,
and JEFFREY L. KEENE

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Appeal No. 1997-2517
Application No. 08/155,102

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ON BRIEF

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Before WINTERS, ROBINSON, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 14, 15, 47-50, and 52, all of the claims remaining in the application. Claim 14 is representative and reads as follows:

> 14. A DNA molecule comprising a recombinant expression system capable, when transformed into a recombinant host cell, of expressing a gene encoding a mutein of the human gonadotropin alpha subunit which mutein, when combined with a beta gonadotropin subunit results in a modified gonadotropin hormone

which is an antagonist to the corresponding native gonadotropin hormone

which expression system comprises an oligonucleotide sequence encoding a human alpha subunit mutein lacking through deletion or alteration one or more of amino acids 88-92 of the native subunit operably linked to control sequences functional in said host cell.

The examiner relies on the following references:

Reddy et al. (Reddy)	4,840,896	Jun. 20, 1989
Clark et al. (Clark)	4,959,455	Sep. 25, 1990

Morell et al. (Morell), "The Role of Sialic Acid in Determining the Survival of Glycoproteins in the Circulation," Journal of Biological Chemistry, Vol. 246, No. 5, pp. 1461-1467 (1971)

Gottlieb et al. (Gottlieb), "Deficient Uridine Diphosphate-N-acetylglucosamine: Glycoprotein N-Acetylglucosaminyltransferase Activity in a Clone of Chinese Hamster Ovary Cells with Altered Surface Glycoproteins," Journal of Biological Chemistry, Vol. 250, No. 9, pp. 3303-3309 (1975)

Merz et al. (Merz), "Studies of the Specific Role of the Subunits of Choriogonadotropin for Biological, Immunological and Physical Properties of the Hormone," Hoppe-Seyler's Z. Physiol. Chem., Vol. 360, pp. 1783-1797 (1979)

Fiddes et al. (Fiddes), "The Gene Encoding the Common Alpha Subunit of the Four Human Glycoprotein Hormones," J. Mol. Appl. Genet., Vol. 1, pp. 3-18 (1981)

Wallace et al. (Wallace), "Oligonucleotide directed mutagenesis of the human β-globin gene: a general method for producing specific point mutations in cloned DNA," Nucleic Acids Research, Vol. 9, No. 15, pp. 3647-3656 (1981)

Parsons et al. (Parsons), "Purification of an Alternate Form of the α Subunit of the Glycoprotein Hormones from Bovine Pituitaries and Identification of its O-Linked Oligosaccharide," Journal of Biological Chemistry, Vol. 258, No. 1, pp. 240-244 (1983)

Matzuk et al. (Matzuk PNAS), "Effects of preventing O-glycosylation on the secretion of human chorionic gonadotropin in Chinese hamster ovary cells," Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 6354-6358 (1987)

Matzuk et al (Matzuk JCB), "Secretion Studies of Chorionic Gonadotropin: The Role of the Carbohydrate Units," Journal of Cellular Biochemistry, Suppl. 0, (11 Part A), p. 280, Abstract E233 (1987)

Bielinska, "Sulfation of the Choriogonadotropin Alpha Subunit in Human Placental Explants," Biochemical and Biophysical Research Communications, Vol. 148, No. 3, pp. 1446-1452 (1987)

Troalen et al. (Troalen), "Antigenic Determinants on Human Choriogonadotropin α-Subunit," Journal of Biological Chemistry, Vol. 263, No. 21, pp. 10370-10376 (1988)

Claims 14, 15, 47, and 49 stand rejected under 35 U.S.C. § 103 as obvious over Matzuk (PNAS) in view of Fiddes, Troalen, Merz, Bielinska, and Wallace.

Claims 14, 15, and 49 stand rejected under 35 U.S.C. § 103 as obvious over Reddy, Fiddes, Troalen, Merz, Bielinska, and Wallace.

Claims 48, 50, and 52 stand rejected under 35 U.S.C. § 103 as obvious over Matzuk (PNAS) in view of Fiddes, Troalen, Merz, Bielinska, and Wallace, further in view of Matzuk (JCB), Morell, Gottleib, Parsons, and Clark.

Claims 47, 48, 50, and 52 stand rejected under 35 U.S.C. § 103 as obvious over Reddy, Fiddes, Troalen, Merz, Bielinska, and Wallace, further in view of Matzuk (JCB), Morell, Gottleib, Parsons, and Clark.

We reverse.

Background

Appellants' specification discloses (pages 1-2) that human gonadotropin a subunit combines with different ß subunits to form several different hormones, including follicle-stimulating hormone, lutenizing hormone, and chorionic

gonadotropin. The specification also discloses (page 2) that genomic and cDNA clones for the a subunit were known in the art. Finally, the specification discloses (page 11) that

> Experiments using chemical derivatization in in vitro assays indicate that amino acids at positions 88-92 (tyr-tyr-his-lys-ser) are necessary for the signal transduction activity of the hormone. Accordingly, deletion or alteration of one or more of these amino acids by site-directed mutagenesis results in analogs which continue to bind receptor but have reduced or negligible activity. All four of the hormones sharing this alpha subunit can thus be prepared as antagonists for the relevant hormone.

Discussion

Claim 14, the only independent claim on appeal, is directed to DNA encoding a mutant human gonadotropin a subunit, where the mutation results in an alteration or deletion of one or more of amino acids 88-92. The examiner rejected all of the claims as obvious over the prior art.

Appellants acknowledge that "the recombinant means to construct the DNA molecules of the invention were available in the art." Appeal Brief, page 22. Appellants also acknowledge that the prior art disclosed a subunit derivatives in which the native a subunit was chemically modified to alter or delete one or more of amino acids 88-92. Appeal Brief, pages 23-24. Appellants argue, however, that the cited references would not have provided the requisite motivation to make the claimed DNA, because the prior art would have led a skilled artisan to expect that an a subunit mutated in amino acids 88-92, combined with a ß subunit, would be unable to bind to its receptor. Appellants argue that a

mutated a/native ß heterodimer would not act as an antagonist for native a/ß hormone unless it bound to its receptor. Therefore, the argument goes, those skilled in the art would not have expected the a subunits encoded by the instantly claimed DNA to be useful as antagonists, nor did the prior art suggest any other use for the mutant a subunits encoded by the claimed DNA. Thus, Appellants conclude, the prior art fails to provide motivation to make the claimed DNA.

The examiner appears to accept Appellants' position that those skilled in the art would have expected a gonadotropin hormone comprising an a subunit mutated at amino acids 88-92 to be unable to bind its receptor. However, the examiner argues that this expectation would not have led to the conclusion that the a subunits encoded by the claimed DNA would be useless as antagonists. The examiner argues that

> the modified a-subunit still binds the ß-subunit and competes with the unmodified a-subunit for the ß-subunit, i.e., it is an antagonist. When the modified a-subunit (as for example where one or more of residues 88-92 is removed . . .) is bound to the ß-subunit, the a/ß dimer is inactive (or at least less active) and is an antagonist of the unmodified a-subunit for the ß-subunit.

Examiner's Answer, page 15. Thus, the examiner's position is that those skilled in the art would have expected that an a subunit having a mutation in amino acids 88-92 would function as an antagonist because, even though a/ß heterodimers comprising such a mutant would not bind to the hormone receptor, the mutant a subunit would compete with native a subunit for binding to the ß subunit and thereby reduce the amount of active a/ß heterodimer.

"It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

> [A] suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . . The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.

In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." Id.

In this case, we find that the references relied on by the examiner do not provide the requisite motivation to produce the claimed DNA. As Appellants argue, the references would have led a skilled artisan to expect that a/ß heterodimers comprising an a subunit with a mutation in amino acids 88-92 would have been biologically inactive and unable to bind to the hormone receptor. See Merz, page 1792 ("The recombination product des-(88-92)-a-subunit + native ß-subunit shows no significant biological activity.") and page 1795 ("The diminution in biological activity therefore seems to be caused rather by a change of the ability to bind to the receptor than by a reduced plasma half-

life."); Bielinska, page 1446 ("[T]he C-terminal region of hCGa plays a critical role in receptor binding of the hormone.").

The examiner argues that a person of ordinary skill in the art would nonetheless have expected the a subunit mutants to be useful as part of a hormone antagonist, because they would compete with the native a subunits for binding to the native ß subunits. This rationale, although creative, is not supported by the cited references. Motivation to combine the prior art must be supported by "actual evidence. That is, the showing must be clear and particular." Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617. The prior art of record does not provide the required evidence.

The references relied on by the examiner provide no suggestion that those skilled in the art would have considered a gonadotropin a subunit mutated at positions 88-92 to be useful as an antagonist in the manner posited by the examiner. Nor do the cited references suggest any other use for the a subunit mutants encoded by the instantly claimed DNA. Since the references do not suggest that the claimed DNA would encode a useful product, they do not provide the required "reason, suggestion, or motivation" to combine their separate teachings in the manner proposed by the examiner.

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art." In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992). Where, as here, the prior art does not support a prima facie case, the

rejection must be reversed. See In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Summary

We reverse the rejections under 35 U.S.C. § 103 because the record lacks evidence showing that a person skilled in the art would have been motivated to combine the cited references.

REVERSED

SHERMAN D. WINTERS Administrative Patent Judge	)
	) BOARD OF PATENT
DOUGLAS W. ROBINSON Administrative Patent Judge	) APPEALS AND
	) INTERFERENCES
ERIC GRIMES Administrative Patent Judge	)

MORRISON & FOERSTER
2000 PENNSYLVANIA AVE. NW
SUITE 5500
WASHINGTON, DC 20006-1812

EG/jlb